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LI, BAO Q

ART UNIT	PAPER NUMBER
1648	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/929,955	SALLBERG ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25 and 28-34* is/are pending in the application.

4a) Of the above claim(s) *26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25 and 28-34* is/are rejected.

7)☒ Claim(s) *21 and 30-34* is/are objected to.

8)☒ Claim(s) *26 and 27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6&7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 21-34 are pending.

Election/Restrictions

1. In response to the previous Office Action on ***Election/Restrictions,*** Applicants cancel all restricted claims 1-20 and file a new set claims 21-34, in which Applicants indicate that all new claims are read on claims 5-12, from which Applicants would elect without traverse of Group V, claims 5-12 in the scope of SEQ ID NO: 16 in Paper No. 11, if they were not canceled.

2. The newly submitted claims 21-34 have been carefully reviewed by the examiner. Upon considering the new claims 21-34, a new restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 21-25 and 28-34, drawn to an immunogenic composition comprising a viral antigen and ribavirin, wherein the viral antigen is a nucleic acid molecule, classified in class 515, subclass 44.

II. Claims 26-27, drawn to an immunogenic composition comprising a viral antigen and ribavirin, wherein the viral antigen is an amino acid molecule, classified in class 424, subclass 189.1.

3. Inventions group I and Group II are unrelated.

4. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of groups I and II are directed to the structurally different components, e.g. the product of Group I is a nucleic acid , whereas the product of group II is protein.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and different sequence or literature searches, the restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Attorney Eric Furman on July 24, 2003 a provisional election was made on traverse to prosecute the invention of Group I, claims 21-25 and 28-34. Affirmation of this election must be made by applicant in replying to this Office action. Claims 26 and 27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 21-25 and 28-34 are considered before the examiner.

Claim Objections

8. Claims 21 and 30-34 are objected to because of the following informalities: the recitation of "a nucleic acid" should be changed as "a nucleic acid sequence or molecule" because an antigen can not be made by a single nucleic acid. An antigen in a nucleic acid form is usually presented as a plasmid DNA, wherein the antigen is encoded at least couple of nucleic acids or a nucleic acid sequence. Therefore, a proper correction is requested.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 21-25 and 28-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17, 34-37 and 84-87 of copending Application No. 10,104,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scopes of the conflict claims are overlapping.

11. In the instant case, claims 21-25 and 28-34 read on a composition and a method for making the composition that comprises a ribavirin and an HCV antigen, wherein the antigen is presented as a nucleic acid molecule, whereas claims 14-17, 34-37 and 84-87 in application SN. 10,104,966 are directed to a composition and method of making the composition that comprises a ribavirin and an HCV antigen. Because an HCV antigen can be broadly explained either as a nucleic acid molecule and an amino acid molecule, the scope of conflict claims are overlapping.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the concentration for the nucleic acid antigen and concentration for the ribavirin and how they are provided in the composition, i.e. the ratio of HCV nucleic acid antigen to the ribavirin etc.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 21 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a composition made by mixing 500 μg of DNA construct encoding rNS3/4A HCV proteins and ribavirin (See disclosure at lines 7-18 on page 65 of specification), does not reasonably provide enablement for having a composition made by any piece of nucleic acid viral antigen, especially a whole HCV virus genome nucleic acid sequence in combination with ribavirin to induce an enhanced immune response after co-administering the composition into the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) & 2) State of art and unpredictability of the filed.

State of art teaches that the DNA vaccine can be made by injecting a plasmid into a host and a plasmid vector encoding HCV antigenic protein but the whole HCV genome is not able to induce an immune response after administering into an animal. However, it is unpredictable whether you inject whole coding sequence of HCV genome into a subject will induce an enhanced immune response or produce a replicating or infectious hepatitis C viral RNA since transfecting a subgenomic HCV into a cell line can produce infectious HCV RNA in vitro as evidenced by Lohman et al. (Science 1999, Vol. 285, pp. 110-113, see abstract) or an acute or persistent infection in vivo as evidenced by Forns et al. (PNAS 2000, Vol. 97, pp. 13318-13323, see abstract). Because claim 29 is directed to use a nucleic acid sequence encoding a whole HCV genome, it is unpredictable that the injection of a whole HCV nucleic acid sequence may be able to produce an infectious HCV RNA particle in a host rather than an immune response.

On the other hand, the art teach that DNA vaccine is usually carried by a plasmid, which must comprise an expression control elements including a promoter and Poly A tail etc. However, the claimed invention is only directed to a nucleic acid in combination of a ribavirin without any detail structural characteristics, it is unpredictable that any piece of DNA without expression control element is able to became an immunogenic composition since a nucleic acid molecule or nucleic acid sequence without expression control elements is unable to express as an antigen polypeptide or peptide.

3) & 4) Number of working examples and amount of guidance.

Applicants only teach that a composition is made by mixing 500 μg of rNS3/4A nucleic acids in a plasmid construct and ribavirin (See disclosure at lines 7-18 on page 65 of specification), which is able to induce an enhanced antibody

However, the specification does not teach any other composition rather than HCV NS3/NS4 nucleic acid sequence, especially the composition comprising the whole HCV nucleic acid molecule, in combination of ribavirin is able to work as an immunogenic composition to induce an immune response when it is administered into an animal.

Applicants present no guidance on how the skilled artisan would practice successfully with the claimed composition to induce an immune response in vivo. Applicants present no guidance how the skilled artisan would address and overcome the art recognized problem as described supra.

5) Scope of the claims.

The claims broad read on a composition comprising any piece of nucleic acid viral antigen, especially the nucleic acid encoding the whole genome of HCV (SEQ ID NO: 13).

6) Nature of the invention.

The invention involves a complex and unpredictable field of HCV DNA immunization.

7) Lever of the skill in the art.

The level of the skill in making HCV immunogenic composition is high.

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 21-25 and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Encke et al. (Intervirology 1999, Vol. 42, pp. 117-124), Tam (US Patent NO. 5,767,097A) and Hultgren et al (J. Gene. Virol. 1998, Vol. 79, pp. 2381-2391).

19. Claimed invention is drawn to use an immunogenic composition comprising HCV antigen and ribavirin, wherein the HCV antigen is a nucleic acid form, which is preferably a non-structural protein NS3 and/or NS4.

20. Encke et al. teach that hepatitis C virus (HCV) non-structural (NS) proteins may play an important role in virus elimination. After 3 intramuscular DNA-based immunizations that encode NS3, NS4 and NS5 in mice, all animals developed detectable antibody responses and generation of inflammatory CD4+ T-cell responses with a predominant TH1 phenotype immune response with all 3 plasmids encoding the NS3, NS4 and NS5 (See lines 12-20 on 2nd col. of page 121). Encke et al. do not teach to use ribavirin in combination of HCV antigen to produce an enhanced immune response.

21. Tam R. teaches that method for produce an immune response, preferentially an enhanced Th1 type immune response to a specific antigen by administering a composition comprising a viral component with a non-viral component of rebavirin into patients (Claims 1-9). Tam et al. does not teach to use HCV antigen for the co-administration.

22. Hultgren et al. teach a method for inducing an enhanced immune response by administering hepatitis viral antigen including HBV e antigen, core antigen and HCV core or non-structural protein NS3 on the basis of daily administering ribavirin 0-1.5 mg per day in mice (See Methods on pages 2382-2383). They demonstrated that the injection of the composition is able to produce an enhanced immune response by increasing the anti-HCV NS3 or Anti-HBe

antibody production or Th1 type of cytokine secretion, such as IL2 or INFγ (See entire section of results, especially Figs. 3-5).

23. Therefore, on the basis of the disclosure of Encke et al. that DNA plasmids encoding HCV non-structural protein NS3-5 are able to induce an immune response to each HCV non-structural protein, which predominantly induce TH1 type immune responses and more importantly, Encke et al. teach that HCV non-structural protein induced immune response are recognized in the art as an important targets for HCV vaccine development, and disclosures by Tam R and Hulgren et al. they both teach that ribavirin favors to increase the TH1 type immune response and increase the antibody production when it is used with a viral antigen, especially HCV antigen to immunize an animal, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by recited references to make an immunogenic composition of HCV made by non-structural protein NS3 and/or NS4 as taught by Encke et al. and in combination with ribavirin to induce an enhance Th1 type immune response as taught by Tam and Hulgren et al. with highly predicted results.

24. Regarding to the limitation of co-administration, the differences between the composition comprising two components of HCV non-structural proteins NS3/NS4 and ribavirin for co-administering at one time and two components of HCV NS3/NS4 and ribavirin administered at one time are only a designed choice since the functions exhibited by the two components as a single mixture administered with one pile or one injection in comparison with administration of the two components at one time but with two separate piles or injections are same. Unless Applicants provide an evidence that these two kinds of administration formula produce significant different results, the claimed invention as a whole is prima facie obvious absence unexpected results.

****

Claims 28 and 29 are deemed free of prior art, given failure of the prior art to teach or reasonably suggest an immunogenic composition comprising nucleic acid sequence of SEQ ID NO: 16 and SEQ ID NO: 13 of HCV viral antigens in combination of ribavirin. However, the claims are not in the condition for allowance because claim 29 is subjected to the ***35 USC §***

1121st paragraph enablement rejection and both claims 28 and 29 are depended on the rejected claim 21.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun LI
July 28, 2003